High Intrarenal Lactate Production Inhibits the Renal Pseudohypoxic Response to Acutely Induced Hypoxia in Diabetes

Intrarenal hypoxia develops within a few days after the onset of insulinopenic diabetes in an experimental animal model (i.e., a model of type-1 diabetes). Although diabetes-induced hypoxia results in increased renal lactate formation, mitochondrial function is well maintained, a condition commonly referred to as pseudohypoxia. However, the metabolic effects of significantly elevated lactate levels remain unclear. We therefore investigated in diabetic animals the response to acute intrarenal hypoxia in the presence of high renal lactate formation to delineate mechanistic pathways and compare these findings to healthy control animals. Hyperpolarized 13C-MRI and blood oxygenation level-dependent 1H-MRI was used to investigate the renal metabolism of [1-13C]pyruvate and oxygenation following acutely altered oxygen content in the breathing gas in a streptozotocin rat model of type-1 diabetes with and without insulin treatment and compared with healthy control rats. The lactate signal in the diabetic kidney was reduced by 12%-16% during hypoxia in diabetic rats irrespective of insulin supplementation. In contrast, healthy controls displayed the well-known Pasteur effect manifested as a 10% increased lactate signal following reduction of oxygen in the inspired air. Reduced expression of the monocarboxyl transporter-4 may account for altered response to hypoxia in diabetes with a high intrarenal pyruvate-to-lactate conversion. Reduced intrarenal lactate formation in response to hypoxia in diabetes shows the existence of a different metabolic phenotype, which is independent of insulin, as insulin supplementation was unable to affect the pyruvate-to-lactate conversion in the diabetic kidney.

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